REMARKS

Status Summary

Claims 1-22 and 37 are pending. Claims 14, 15, and 19 are withdrawn from consideration as being directed to a non-elected species. Claims 1-13, 16-18, 20-22, and 37 were examined.

Claims 1-13, 16-18, 20-22, and 37 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,695,770 to Raychaudhuri et al. and Hoefer et al. (1995) *Cancer Immunol Immunother* 41:302-308. Claim 17 is objected to for grammatical error. The specification is objected to for incomplete reference to the priority application. Reconsideration in view of the following amendments and remarks is respectfully requested.

Objection to the Specification

The specification is objected to for incomplete reference to the priority application. Office Action, page 3. The reference to priority application U.S. Serial No. 08/933,359 is amended to clarify its status as now abandoned. The status of the instant application is also corrected to properly identify it as a divisional of U.S. Serial No. 08/933,359 since both applications are drawn to the same elected subject matter.

Objections to the Claims

Claim 17 is objected to for reciting "wherein said immunosuppressive factors is TGFβ," which is grammatically incorrect. Office Action, page 3. Claim 17 has been amended to correct the noted error.

Rejection of Claims Under 35 U.S.C. § 103(a)

Based on Raychaudhuri and Hoefer

Claims 1-13, 16-18, 20-22, and 37 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,695,770 to Raychaudhuri et al. (Raychaudhuri) and Hoefer et al. (1995) *Cancer Immunol Immunother* 41:302-308 (Hoefer). Office Action, pages 3-6. This rejection is traversed for the reasons set forth below.

Raychaudhuri describes antigen formulations useful for inducing a cytotoxic T lymphocyte response (CTL), which formulations include a stabilizing detergent, a micelle-forming agent, and/or an oil. The examiner notes that Raychaudhuri does not teach antigen formulations that further include at least one agent for down regulating the activity of an

immunosuppressive factor, such as TGFβ. Office Action, page 5, ¶ 1. Hoefer describes anti-TGFβ antibodies that can suppress development of primary tumors and metastases by down regulation of MHC-unrestricted cytotoxicity. In the view of the examiner, it would have been *primae facie* obvious to combine the antigen formulation of Raychaudhuri with the TGFβ antagonist (antibody) of Hoefer into a single composition because each agent has been taught in the prior art to be useful for the treatment of cancer. Office Action, page 5, ¶ 3. The examiner's rationale relies on *In re Kerkhoven*, in which the Court of Customs and Patent Appeals held that preparation of a composition is obvious when prepared by combination of two compositions which are individually useful for the same purpose. Office Action, page 6, ¶ 1.

The examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143.

The Court of Appeals for the Federal Circuit has repeatedly held that secondary considerations such as unexpected results can effectively rebut a finding of *primae facie* obviousness. *See e.g.*, *In re Geisler*, 116 F.3d 1465, 1469, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Thus, even assuming *arguendo* that a *primae facie* case of obviousness has been established, the unexpected and synergistic qualities of the presently claimed combination are sufficient to overcome the examiner's finding.

In the application of *Kerkhoven*, applicants claimed a method for producing particulate detergent compositions containing a mixture of anionic and nonionic active detergent materials. Kerkhoven's claims were rejected on the basis that "the mere mixing of two compositions each taught for the same purpose, in the absence of a showing of unexpected results, is obvious." *In re Kerkhoven*, at 849.

The present invention provides a composition for enhancing tumor immunity that combines a cytotoxic T lymphoctye (CTL)-inducing vaccine and one or more agents that are capable of neutralizing, antagonizing, down regulating or blocking tumor-secreted immunosuppressive factors, such as TGFβ (*see e.g.*, page 4, lines 1-7). A CTL-inducing

vaccine comprises an antigen formulation, particularly an microfluidized antigen formulation comprising (i) a stabilizing detergent, (ii) a micelle-forming agent, and (iii) a biodegradable and biocompatible oil, as recited in step (a) of each of claims 1 and 37. Such antigen formulations are described in U.S. Patent No. 5,585,103 and are referred to as "PROVAX™" compositions (*see e.g.*, page 2, line 18 through page 3, line 4).

In contrast to the combination of *Kerkhoven*, the instant application discloses the surprising result that the combination of an antigen formulation as recited in the claims and at least one agent that neutralizes or down regulates immunosuppressive factors has an unexpected quality not predicted by the mere sum of the individual agents, *i.e.* a capability to elicit an enhanced therapeutic response (*see e.g.*, page 6 lines 16). Example 1 discloses that co-administration of an ovalbumin antigen formulation in conjunction with anti-TGFβ antibodies elicited anti-tumor activity under conditions where treatment with the ovalbumin antigen formulation alone was ineffective (page 16, lines 18-22; Figure 1). Similarly, Example 2 describes enhanced anti-tumor activity via co-administration of an E7 antigen formulation and anti-TGFβ antibodies (page 18, lines 6-8; Figures 2A and 2B).

To clarify the unexpected qualities of the claimed combination, claim 1 is amended herein to recite an antigen formulation having an ability to induce a cytotoxic T lymphocyte response that when combined with an agent for neutralizing or down regulating immunosuppressive factors is capable of a inducing a cytotoxic T lymphocyte response that is enhanced relative to a cytotoxic lymphocyte response induced by said antigen formulation. Claim 37 is similarly amended to recite the enhanced therapeutic properties of the disclosed combination. In accordance with *In re Geisler*, the synergism between the disclosed antigen formulation and an agent for neutralizing or down regulating an immunosuppressive factor is strong evidence that the claimed combination is unobvious.

Based on the foregoing arguments, applicants believe that claims 1 and 37 are patentable over the cited references in accordance with 35 U.S.C. § 103(a). Specifically, the deficiency of Raychaudhuri is not cured by the description of anti-tumor activity of a TGFβ antagonist in Hoefer because the combined references do not suggest a greater-than-additive anti-tumor activity as recited in claims 1 and 37. Claims 2-13, 16-18, and 20-22 ultimately depend from claim 1 and are therefore also believed to be unobvious over the prior art. Thus, applicants respectfully request that the withdrawal of the rejection of claims 1-13, 16-18, and 20-22 under § 103(a) be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner believes may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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